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13.4
Research Involving Human Subjects

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New document or new requirements

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☒ **New document**
☐ **Major requirement change**
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13.4

Research Involving Human Subjects*

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*New document

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Research Involving Human Subjects

1.0 Introduction

1.1 Laboratory Program

Lawrence Livermore National Laboratory is required by federal law to review and approve all research projects involving human subjects. For such research, the Laboratory adopts the requirements established in 45 CFR 46 (Protection of Human Subjects), as formulated by the Department of Health and Human Services (DHHS). The Laboratory also adopts the ethical principles for research with human subjects set forth in the Belmont Report, published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (For more information about the Belmont Report, see Section 6.2.)

1.2 Purpose and Scope

The LLNL Institutional Review Board (IRB) was established and is supported by the Laboratory Director as part of his assurance to the DHHS and the Department of Energy that LLNL complies with federal regulations pertaining to the protection of human subjects involved in research projects at the Laboratory. Details about this assurance are available at the following Internet address:

http://www.llnl.gov/HumanSubjects/mpa.html

All proposed research projects that involve human subjects, their bodily materials, or their personal, private information shall be reviewed by the IRB to assess the relative benefits and risks to the human subjects prior to the initiation of research. Research as it applies to human subjects is defined in 45 CFR 46.102 (d) as follows:

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Persons unsure of whether an activity constitutes human research are encouraged to contact the IRB Office. Additional guidelines regarding the types of activities that may or may not be considered research can be found at the following Internet address:

http://www.cdc.gov/od/ads/opspoll1.htm

This document and the IRB's Web site (http://www.llnl.gov/HumanSubjects/) contain key information about the IRB and federal regulations that govern research activities involving human subjects. In addition, the IRB's Web site provides detailed information for researchers (i.e., Principal Investigators and key personnel identified by Principal Investigators) who are using, or contemplating the use of, human subjects in their research projects. This information is available at the following Internet address:

http://www.llnl.gov/HumanSubjects/bg-info.html#sec1

The IRB's Web site is updated frequently and should be consulted regularly. Appendix A contains a list of acronyms, terms, and definitions used in this document.

1.3 General Requirements

All research involving human subjects shall be reviewed and approved by the IRB before research can be initiated. This requirement applies to all research involving human subjects and all activities that even in part involve such research, regardless of sponsorship, if one or more of the following apply:

- The activity is sponsored, in part or entirely, by LLNL.
- Some or all of the activity is conducted by, or under the direction of, any LLNL employee or subcontract worker in connection with his or her Laboratory duties.
- Some or all of the activity is conducted by, or under the direction of, any LLNL employee or subcontract worker using any LLNL property or facility.
- The activity involves the use of LLNL's nonpublic information to identify or contact human research subjects or prospective subjects.

The term "human subjects research" covers a broad range of activities. The following list provides a few examples of research activities that require IRB review and approval:

- The use of human-derived data.
- The use of cultures of human cells.
- Projects or pilot studies in which the investigator is the only subject.
- Research projects in which information is sought or obtained either directly from the subject (e.g., through an interview or questionnaire) or indirectly (e.g., through observation of human subjects or access to identifiable private records).

- Collaborative studies in which human material or information is collected at another institution and sent to researchers at the Laboratory.
- Requests for information from third parties interested in conducting human subjects research or concerning existing human subjects research.
- Donation of tissues, organs, fluids, or other bodily material.
- Research projects that require human subjects to participate in physical activities.
- Evaluation of medical devices that are being developed to evaluate health or detect disease. [Medical device studies are also regulated by the Food and Drug Administration (FDA).] Additional information is available at the following FDA Web site:

  http://www.fda.gov/cdrh/devadvice/11.html

2.0 Hazards

The hazards associated with research involving human subjects vary according to the specific research protocol and the nature of the work. Responsible Individuals shall be aware of potential hazards in research protocols and develop safeguards to protect the research participants against those hazards. All members of the research team bear the ultimate ethical responsibility for their work with human subjects. Society entrusts researchers with the privilege of using other humans to advance scientific knowledge. In return, society expects researchers to show respect for those subjects.

Three basic ethical principles are particularly relevant to research involving human subjects: respect for persons, beneficence, and justice. To apply these principles when planning and conducting research involving human subjects, the research team needs to consider the hazards described in this section.

2.1 Identification of Research Hazards

One of the responsibilities of a Principal Investigator is to ensure that the risks of the research are outweighed by the anticipated benefits to the subjects or by the importance of the knowledge that may reasonably be expected as a result of the research. Commonly recognized risks are psychological or physical pain and injury. Other types of potential risk that should not be overlooked include privacy and confidentiality issues; legal and social harm; and loss of insurance or employment or other economic harm.

2.2 Assuring Informed Consent

Researchers shall provide subjects with sufficient information to make an informed decision as to whether or not to participate in the research activity and are responsible for ascertaining that subjects comprehend the information. Without comprehension of a project and its potential risks, the human subject cannot provide informed consent. Finally, an agreement to participate in research constitutes valid consent only if given voluntarily. Consent to participate shall be free of coercion and undue influence.

2.3 Equitable Selection of Subjects

Individuals asked to participate in the research should be broadly representative of the target research population. Therefore, research subjects shall be selected in such a manner to assure that no classes of persons (e.g., employees, subordinates, students, racial or ethnic minorities, or welfare patients) are being systematically selected simply because of their availability, compromised position, or manipulability, rather than for reasons directly related to the problem being studied.

3.0 Controls

All research projects involving human subjects require review and formal approval by the LLNL IRB. The main purpose of this review is to determine whether subjects are at risk, whether the potential benefits of the research outweigh the risk, and whether adequate provision has been made to obtain informed consent. Ongoing reporting requirements apply for all human subjects research activities. Information about the IRB review and approval process is available at the following Internet address:

http://www.llnl.gov/HumanSubjects/bg-info.html#sec2

3.1 Submitting a Protocol for IRB Review

Prior to preparing a protocol for review, Principal Investigators should consult the IRB's Web site and then discuss the following issues with IRB Office personnel:

- The type of review required.
- Any documentation necessary for the review.
- The review schedule.

There are two types of IRB review: full Board review and expedited review. Research involving no more than minimal risk may be eligible for an expedited review by one or more Board members. Expedited reviews take place outside of (i.e., do not require) a

convened IRB. A protocol that does not meet the federally defined criteria for expedited review is reviewed by the full Board during a regularly scheduled IRB meeting at which a quorum of Board members are in attendance.

Investigators shall submit the appropriate protocol review forms to the IRB Office when requesting new or continuing review of a human subjects research activity. The forms are listed in Table 1 and are available at the following Internet address:

http://www.llnl.gov/HumanSubjects/forms.html

Table 1. Forms to submit for reviews of human subjects research activity.

Type of activity	Form to submit
New protocol	**"Request for Review"** **"New Protocol Application"**
Annual review	**"Request for Review"** **"Renewal Application"**
Protocol amendment or modification	**"Request for Modification/Amendment"**
Exempt research	**"Request for Exempt Research Determination"**

Additional information about IRB reviews, including preparations for and types of review, is available at the following Internet address:

http://www.llnl.gov/HumanSubjects/humsubj.html#sec2

3.2 Ongoing Reporting Requirements for Approved Research

All research using human subjects shall receive continuing review at an interval not to exceed 12 months. Research involving more than minimal risk may require more frequent review.

After a protocol has been approved by the IRB, the Principal Investigator has ongoing reporting responsibilities and shall obtain IRB approval for all changes to the protocol before any changes can be implemented. For example, an amended protocol is required when the investigator proposes to involve human subjects in ways different from those approved in the original protocol. IRB review is also required in the event of any changes in any of the forms seen by the subjects or changes in the types, or increases in the number, of subjects. All proposed changes shall be approved in writing by the IRB.

3.2.1 Reporting of Adverse Events

Any injuries, unanticipated problems, or noncompliance with the requirements of the approved protocol shall be reported to the IRB chair within 10 calendar days of discovery. Any potentially serious, unanticipated complication affecting a subject requires immediate reaction by the research team to help mitigate any harm sustained and to prevent further harm.

In addition, the Principal Investigator shall report to the IRB chair any injuries, illnesses, or other unanticipated complications possibly related to the research. This reporting shall take place within 10 calendar days of discovery.

Information about continuing review and ongoing reporting requirements is available at the following Internet address:

http://www.llnl.gov/HumanSubjects/humsubj.html#ongoing

3.3 Research Activities Exempt from Federal Regulations

If the human subject involvement in a research project satisfies certain criteria, and the investigator believes the research activity is exempt from federal regulations governing research involving human subjects, the investigator should submit a Request for Exempt Research Determination form to the IRB Office. If the research activity is determined by the IRB Office staff to be exempt from further review, the IRB Office issues a Notice of Exempt Determination. Additional information about exemption is available at the following Internet address:

http://www.llnl.gov/HumanSubjects/bg-info.html#exempt

3.4 Training

All researchers at LLNL who are engaged in research involving human subjects shall successfully complete the Web-based course HS0035-W (Human Subjects Research Training) at:

http://www-training.llnl.gov/wbt/hc/HS0035/HSR01.html

Researchers engaged in research involving human subjects shall repeat this course every two years to stay abreast of changes in regulations and procedures. Additional training is provided by the IRB Office staff on an as-needed basis.

All individuals who develop protocols for submission to the IRB are required to read the "Responsibilities of Principal Investigators for Research Projects Involving Human Subjects" section of the Web site and to certify that they have done so when they submit their protocol.

4.0 Responsibilities

LLNL, the IRB, the IRB Office staff, and Principal Investigators all share responsibility for the proper review of research involving human subjects. Additionally, all research team members are responsible for the ethical conduct of their research. The responsibilities are outlined in detail in the IRB document "Multiple Project Assurance of Compliance with the DHHS Regulations for the Protection of Human Research Subjects," available at the following Internet address:

http://www.llnl.gov/HumanSubjects/mpa.html

4.1 Laboratory Director / Authorized Institutional Official

The Laboratory Director, or the person to whom the Director has delegated Authorized Institutional Official (AIO) authority, is responsible for the performance of all LLNL research involving human subjects. The AIO also establishes an IRB and provides meeting space and IRB Office staff to support the IRB's review and recordkeeping duties.

4.2 Institutional Review Board Office

The IRB Office staff is responsible for:

- Facilitating interactions between the IRB and researchers.
- Determining whether a research activity is subject to IRB review and, if so, what level of review is appropriate. The three possible levels of review are
  - — Exempt from review.
  - — Expedited review.
  - — Full Board review.
- Maintaining IRB records and acting as a point of contact for audits.
- Interacting with the Department of Energy (DOE), the University of California Office of the President, other federal and state departments and agencies, and other IRBs in matters regarding research involving human subjects. [Any issues associated with exemption from, or interpretation of, the requirements are addressed by the Work Smart Standards Change Control

Board in accordance with Document 2.3, "LLNL Exemption Process," in the *Environment, Safety, and Health (ES&H) Manual*.]

- Providing information and education concerning regulations and guidelines covering research involving human subjects.
- Reporting significant adverse events or serious or continuing noncompliance with regulations to the appropriate institutional officials, as named in Section 4.1, the DHHS's Office for Human Research Protections, and the head of any other sponsoring federal department or agency.

4.3 Institutional Review Board

The IRB is responsible for ensuring that a research activity includes processes for protecting the rights and welfare of human subjects by:

- Evaluating proposed research activities.
- Approving, or requiring modification to, research protocols.
- Conducting continuing review of active protocols (at least annually).

4.4 Responsible Individuals

For human subjects research, the Responsible Individual, as defined in the LLNL Integrated Safety Management System (ISMS), is the Principal Investigator.

Principal Investigators are responsible for:

- Understanding the ethical principles and regulatory guidelines governing research activities involving human subjects, including investigator financial conflicts of interest (covered in Course HS0035-W, available online at http://www-training.llnl.gov/wbt/hc/HS0035/HSR01.html).
- Understanding applicable regulatory requirements, including 45 CFR 46 and regulations governing FDA-regulated medical devices, drugs, and biologics (covered in HS0035-W).
- Protecting the rights and welfare of human subjects who participate in research (as described in the Belmont Report) by obtaining proper informed consent from the subjects.
- Recognizing that IRB review and approval shall precede any work involving human subjects.
- Identifying all activities that have a research component involving human subjects.

- Identifying all key personnel who require human subjects research training (i.e., HS0035-W).
- Notifying the IRB Office of their intention to use human subjects in research.
- Submitting to the IRB Office the material required to facilitate review of research.
- Requesting IRB approval of any changes to a research protocol prior to implementation of those changes.
- Notifying the IRB Office within 10 calendar days of discovery of any injuries or other unanticipated problems or noncompliance with the requirements of an approved protocol.

5.0 Work Smart Standards

45 CFR 46, "Protection of Human Subjects," codified and adopted by DOE on June 18, 1991 as 10 CFR 745. Refer to the following Internet address:
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

21 CFR 50, "Protection of Human Subjects" (FDA). Refer to the following Internet address:
http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr50_99.html

21 CFR 56, "Institutional Review Boards" (FDA). Refer to the following Internet address:
http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr56_99.html

6.0 Resources for More Information

6.1 General Information

Information about the Laboratory's IRB and research involving human subjects can be obtained by contacting the IRB Office. Key information about the IRB and federal regulations that govern research activities involving human subjects is also available at the following Internet address:

http://www.llnl.gov/HumanSubjects

This Web site is designed to be used by researchers who are currently using, or contemplating the use of, human subjects, their bodily materials, or human-derived data in their research projects.

6.2 Other Sources

DOE Order 443.1, "Protection of Human Subjects." Refer to the following Internet address:

http://www.directives.doe.gov

"The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research," National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979. Refer to the following Internet address:
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm

Appendix A

Acronyms, Terms, and Definitions

Adverse event	Any incident that is inconsistent with the approved protocol or any injury or unintended adverse impact to a subject as a result of participation in the research activity.
Human subject	A living individual about whom an investigator conducting research obtains either of the following: • Private, identifiable information. • Data through intervention or interaction with the individual.
Informed consent	A subject's consent to participate in research based on a full understanding of the research and any attendant risks or benefits.
Institutional Review Board (IRB)	An institutional committee established in accordance with, and for the purposes expressed in, the regulations and standards listed in Section 5.0 of this document.
IRB	See "Institutional Review Board."
Minimal risk	Risk in which the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
Research	A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.
Researcher	The Principal Investigator or key personnel identified by the Principal Investigator as having sufficient involvement in the human subjects research activity to require formal training in human subjects research (i.e., Course HS0035-W).